Postepy Hig Med Dosw. (online), 2007; 61: 461-465
e-ISSN 1732-2693

www.phmd.pl
Original Article

Received: 2007.07.04
Accepted: 2007.07.30
Published: 2007.08.03

Phage therapy of staphylococcal infections (including MRSA) may be less expensive than antibiotic treatment

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

The current drama of antibiotic resistance has revived interest in phage therapy. In response to this challenge, a phage therapy center was established at our Institute in 2005 which accepts patients from Poland and abroad with antibiotic-resistant infections. We now present data showing that efficient phage therapy of staphylococcal infections is no longer a treatment of last resort (when all antibiotics fail), but allows for significant savings in the costs of healthcare.

Key words: phage • MRSA • cost of therapy • staphylococcal infection

Full-text PDF: http://www.phmd.pl/pub/phmd/vol_61/10883.pdf
Word count: 1921
Tables: 2
Figures: –
References: 39

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Lack of new antibiotics requires re-evaluating and re-investing in bacteriophages.
(Bradley J.S., Guidos R., Baragona S., Bartlett J.G., Rubinstein E., Zhanel G.G. et al.: Anti-infective research and development – problems, challenges, and solutions. Lancet Infect. Dis., 2007; 7: 68–78)

Introduction

Bacterial infections of different tissues and organs that prove incurable by antibiotics are a serious clinical problem. This is caused in large by the increasing prevalence of antibiotic-resistant bacteria, mainly resulting from the extensive use of antibiotics. For example, *Staphylococcus aureus* may be resistant not only to methicillin (MRSA), but also to vancomycin (VRSA) [22,25]. Furthermore, researchers are beginning to question the continued utility of vancomycin for MRSA infections [15]. Moreover, Gram-positive bacteria resistant to linezolide and chinupristin/dalfopristin, antibiotics introduced recently for the treatment of infections by vancomycin-resistant strains, have also been described [18,21,38]. Similar problems are observed in the therapy of infections caused by Gram-negative bacilli of the *Enterobacteriaceae* family that produce extended-spectrum β-lactamases, and some strains of multidrug-resistant *Pseudomonas aeruginosa* producing metalloenzymes are often sensitive only to the toxic colistine [8,20,24]. The problems caused by such dangerous bacteria also concern Poland. The isolation of an *Enterococcus faecium* strain resistant to vancomycin and linezolide from a patient at a hematological unit in Poland has been described [12].

Under unfavorable conditions, such as contamination with a multidrug-resistant strain, dysfunction of the immune system, or advanced age, bacterial infection may be a considerable risk to a patient's health, or even life [5,29,32]. For instance, MRSA, whose carriage seem to be rising rapidly, is responsible for suppurative skin and soft tissue infections and postoperative wound infection [6,23,37]. It may also cause organ or systemic infections, such as brain abscess, osteomyelitis, pneumonia, meningitis, and life-threatening bacteremia [1,11]. In addition, an increasing proportion is not caused by hospital infections, but is community acquired [16]. For this reason an effective treatment of local infections prevents many serious and even tragic complications.

The World Health Organization, the European Parliament, the US Food and Drug Administration, and many scientific organizations the world over acknowledge the elimination of drug resistance of microbes as a priority action. However, current analyses show that the search for new anti-infection agents conducted by pharmaceutical companies is becoming more and more restricted due to the growing costs of conducting the appropriate trials, low profits, and high risk of the investment precisely because of the possibility of rapid acquisition of resistance to the new drug [4,19,36]. Because the antibiotic pipeline threatens to run dry, the role of academic centers and scientific institutions supported by government funds in developing new anti-infection technologies is becoming increasingly crucial. Among the methods alternative to antibiotics and chemotherapeutics for combating bacterial infections, therapy using bacteriophages is frequently mentioned [3,7,14,26,30,31].

Bacteriophages (or simply "phages") are bacterial viruses which attack bacteria, multiply within them, and then destroy them. They are "programmed" to destroy one or a few kinds of different strains of bacteria. Phages are widespread in nature and can appear naturally in food and in the human body (for example in the intestines). Phages can efficiently destroy bacteria which have acquired resistance to antibiotics and which cause life-threatening infections [2,17,33,34]. It is this exceptional feature which determines whether to apply phages in treating bacterial infections.

The method of treating bacterial infections using phages has been known since the beginning of the 20th century and is applied in several medical centers [3,27]. In the experimental studies to date, the method has usually been used in cases in which antibiotic treatment did not bring improvement. The Institute of Immunology and Experimental Therapy of the Polish Academy of Sciences in Wrocław has been conducting research on the biological properties and the application of bacteriophages for several decades [28,35]. The phage formulations produced by the Institute can be used in patients infected with bacteria of the genera *Staphylococcus*, *Enterococcus*, *Escherichia*, *Citrobacter*, *Enterobacter*, *Klebsiella*, *Shigella*, *Salmonella*, *Serratia*, *Proteus*, *Pseudomonas*, and *Stenotrophomonas*. The rate of successful typing of *Staphylococcus* in the Bacteriophage Laboratory is around 80%.

At the end of 2005 the Phage Therapy Center at the Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, was opened. The purpose of this therapy is to treat, with the aid of bacteriophages, patients with non-healing postoperative wounds or bone, upper respiratory tract, urinary, or reproductive tract infections in whom extensive antibiotic therapy failed or the use of the targeted drug is contradicted.

According to Polish law, phage therapy is considered an experimental treatment which is carried out on the basis of the respective legislation (pharmacological law, regulations of the Minister of Health). Experimental treatment (or, translated literally, *a therapeutic experiment*) occurs when a physician introduces new or only partially tested diagnostic, therapeutic, or prophylactic methods for the direct benefit of the person being treated. In contrast, an investigational experiment has the primary purpose of broadening medical science (and is tantamount to clinical research). To satisfy the existing requirements, two basic items are prerequisites for experimental therapy: a) the written informed consent of the patient and b) approval by an institutional review board (bioethics commission). Furthermore, it may be implemented only by a qualified doctor and when available treatment has failed (arts. 29/1, 21/2, and 21/3 of the law on the physician's profession). Therefore, our current therapy involves cases in which prior antibiotic treatment did not lead to the eradication of infection [10].

The aim of our communication is to present briefly the economic aspects of the experimental phage therapy on the basis of our own data obtained from patients infected with *Staphylococcus* and treated at the Phage Therapy Center.

Table 1. The mean calculated approximate cost of the staphylococcal infection treatment (6.5 week) at the Phage Therapy Center in Wrocław

Position	Mean cost [PLN]	Minimal cost [PLN]	Maximal cost [PLN]
Medical service[a]	858	550	1600
Laboratory tests[b]	452	262	776
Bacterial culture[b]	112	42	210
Medication for neutralization of stomach acid[c]	44	0	102
Service of the Bacteriophage Laboratory:[d]			
– phage typing	147	80	240
– phage preparations	483	200	1200
Total	**2096**		

[a] calculated according to the price list of the Phage Therapy Center from Feb. 11, 2007;
[b] calculation based on the price of service of local diagnostic laboratories;
[c] quote was calculated for Alugastrin (dihydroxialumini sodium carbonate) in a 250-ml suspension based on data obtained June 20, 2007 from the official web site of PROSPER S.A.;
[d] calculated according to the price list of the Bacteriophage Laboratory services from Feb. 1, 2007.

Patients and Methods

We have analyzed the approximate cost of treating staphylococcal infection on the basis of six cases in which good clinical effect of the phage therapy was seen. Typically, the phages are administered orally (one 10-ml ampoule three times daily after neutralization of gastric juice) and/or locally (one ampoule two times daily for wet compresses, throat wash, or irrigation of the fistula) in the form of phage lysates. These patients (3 males and 3 females, aged from 30 to 76 years) included two cases of MRSA infection (osteomyelitis and pharyngitis), one case of methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) infection, and three cases of MSSA (methicillin-sensitive *S. aureus*) infection in whom targeted antibiotics proved to be ineffective (breast abscess, soft tissue infection, and respiratory tract infection). The patients' clinical data and detailed results of the treatment will be the subject of a separate publication.

The total cost of the therapy included the costs of the medical service (qualification for the treatment and control visits), laboratory and diagnostic tests (including the panel of obligatory tests included in our Treatment Protocol), bacterial culture, phage typing, preparation of the phage formulation, and the costs of medication for neutralizing stomach acid (typically, Alugastrin in suspension). (Because of the differences in the costs for services provided to foreign patients, their costs are calculated on the basis of a separate price list which was not considered in our analysis). The mean calculated approximate cost of each analyzed element as well as the total mean cost of the staphylococcal infection treatment are shown in Table 1 (the data are valid for Polish patients; foreign patients must bear slightly higher costs, which are not presented here).

Results

The mean duration of phage therapy was 6.5 weeks and its total cost was 2,096 PLN (1 EUR = approx. 4 PLN). In previous studies presented by Ślopek et al. and Weber-Dąbrowska et. al. [25,35], the mean time of the therapy was 35 and 32 days, respectively (range: 1–12 weeks). According to our simulations, the cost of each additional treatment (if needed) is about 483 PLN per 3 weeks.

The lowest total cost (1,444 PLN) was associated with the treatment of pharyngitis (throat wash with phage preparation was administered) caused by MRSA which lasted 4 weeks. The costs of treatment of MSSA soft-tissue infection (shin wound, 6 weeks of oral phage application), MRSA bone infection with chronic fistula (5 weeks of oral phage application), breast abscess caused by MSSA (6 weeks of oral phage application), and MSSA infection of the respiratory tract (4 weeks of oral phage application) ranged from 1,5203 PLN to 2,141 PLN. The highest total cost (4,044 PLN) was associated with the treatment of post-operative wound infection by MRCNS, which generally lasted a total of 13 weeks (the patient underwent two courses of phage therapy lasting 7- and 6-weeks; the phage preparations were administered both orally and locally).

In Table 2 we present some data on the most expensive antibiotics on the Polish market recommended for the therapy of multidrug-resistant staphylococcus infection (based on the "Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK") [9]. We have calculated only the putative cost of each drug for a 10-day therapy to enable comparison with the costs of phage therapy. The analysis shows that the use of vancomycin is the least expensive (1376.00 PLN – 2076.20 PLN), while the medium cost (6235.42 PLN – 7562.80 PLN) is for linezolide and chinupristin/dalfopristin and the highest for teicoplanin (10,483.40 PLN). As may be seen in Table 1, the mean cost of the phage preparations used in the therapy is comparably low (483 PLN) and the mean cost of all the "essential" elements of phage therapy, such as the phage preparation, Alugastrin, bacterial culture, and phage typing, was 786 PLN for the treatment of staphylococcal infection with good clinical effect. This is about half the cost of 10-day therapy with vancomy-

Table 2. The most expensive drugs used in the therapy of MRSA infection on the Polish market

International drug name	Main indications[a]	Adult dose Time of treatment	Trade name, route of administration, dose, number of vials	The wholesale price for pharmacy[d]	Cost of 10 days of therapy
Vancomycin	Bacteremia Serious soft tissue infections Bone infection	2 g/day 7–28 days	EDICIN *i.v.* 1 g × 1 vial	68.8 PLN	1376.00 PLN
			VANCOCIN CP *i.v.* 1g. × 1 vial	103.66 PLN	2073.20 PLN
Linezolide	Pneumonia Serious soft tissue infections Bacteremia GISA[b] and GRSA[c] infection	600 mg × 2/day 10–14 days	ZYVOXID *i.v.* 2 mg/ml × 10 vials	3568.18 PLN	7136.36 PLN
			ZYVOXID *p.o.* 600 mg × 10 tablets	3117.71 PLN	6235.42 PLN
Teicoplanin	Serious soft tissue infections Bacteremia (but loading doses essential and adequate levels unpredictable)	400 mg/day 7–10 days	TARGOCID *i.v.* 200 mg × 1 vial	524.17 PLN	10483.40 PLN
Chinupristin + Dalfopristin	Reserve drug GISA[b] and GRSA[c] infections	500 mg × 2/day 7–10 days	SYNERCID *i.v.* 150 mg + 350 mg × 1 vial	378.14 PLN	7562.80 PLN

[a] Based on "Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK" [9];
[b] Glycopeptide intermediate-resistant *S. aureus*;
[c] Glycopeptide-resistant *S. aureus*;
[d] Data obtained June 20, 2007, from the official web site of the pharmaceutical distributor PROSPER S.A.

cin and several times less compared with the other drugs shown in Table 2.

Discussion

In 1963, Witoszka and Strumiłło, from one of the leading surgical clinics of Poland directed by Professor Jan Nielubowicz, described their results of local treatment with phages of postoperative wounds infected with coagulase-positive staphylococcus resistant to common antibiotics [39]. The authors reported a 70% success rate (35 of their 50 patients responded to the phage therapy), which corresponded to the effectiveness of the treatment with expensive antibiotics. Despite the great progress and introduction of new antibiotics since that time, the relative costs of the treatment of infection by drug-resistant bacteria are still very high.

The "strongest" (and the most expensive) antibiotics which are used in the treatment of MRSA infections, such as vancomycin, teicoplanin, and chinupristin/dalfopristin, can be administered only intravenously during the patient's hospital stay, and this significantly augments the total cost of treatment. Only linezolide has a formulation that enables oral administration in outpatients, but the cost of this therapy is over 6,000 PLN, which is higher than the total mean cost of a 6.5-week phage therapy (including the costs of medical service and diagnostic tests). Our phage preparations can be administered to the patients orally and/or locally. This enables us to conduct phage therapy in outpatients, which is very important in chronic infections. Patients with chronic infections often need prolonged administration of antibiotics, which may significantly augment total costs. Phage therapy, due to its chronic character and the good tolerance of phages even in the form of lysates, can be particularly recommended for these patients.

Conclusions

In conclusion, it seems that the experimental phage therapy could be an alternative to antibiotics (and replace them when they fail) for the treatment of chronic MRSA infections, especially in outpatients. The treatment may help prevent the introduction of potentially lethal infections into the hospital environment. Recently we described a case of the successful eradication of MRSA carrier status in a healthcare worker [13]. This is of great importance in view of the emerging problem of not only hospital-acquired MRSA (HA-MRSA), but also community-acquired MRSA (CA-MRSA) [9,15]. Moreover, the significantly lower costs of phage therapy constitute an important additional argument for its wider consideration in the current era of a worldwide crisis in antibiotics resistance and the economics of healthcare.

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